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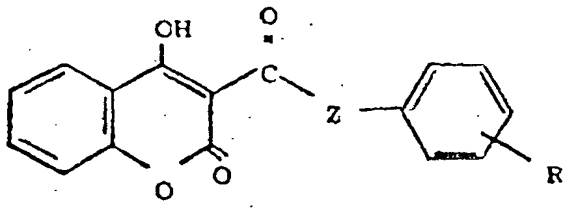
(54) **New antithrombotics derived from coumarin and procedures for its obtainment.**

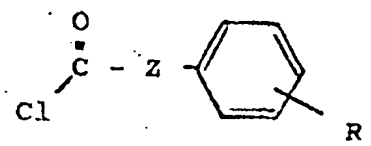
(57) New antitrombotic derivatives of coumarin and procedures for obtaining them. Said derivatives responri to the formula (I) wherein Z and R are as indicated in the description.

The compounds are prepared by acylation of 4-hydroxycoumarin with an acid chloride of formula (II).

The compounds obtained are useful as antitrombotic agents for the prevention and the treatment of coronary and trombolitical diseases.




(I)




(II)

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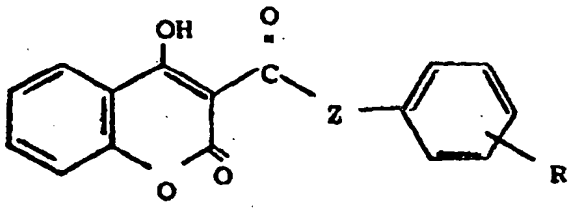
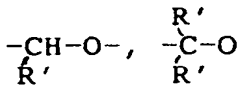
The present invention concerns new derivatives of hidroxy-4-coumarin, of the general formula



(I)

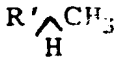
wherein:

z can be $(CH_2)_n$-, $(CH_2)_n$-0-,



n = 1 or 2

being



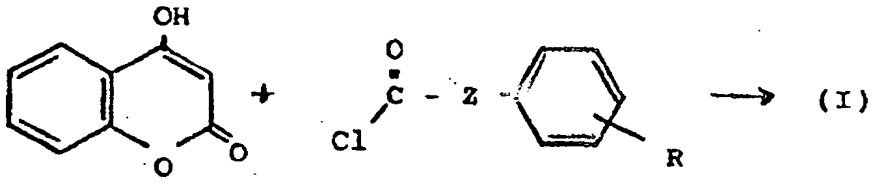
or $C_2H_5$

R can be: H, $CH_3$, $C_2H_5$, Cl, Br, F, $NO_2$, $CF_3$.

The position of R is preferably for or goal.

These derivatives are resultant of the acylation in 3 of the hidroxy-4-coumarin.

The general preparation procedure consists in effecting the acylation with an acid chloride according to the following scheme:



The reaction is preferably effected in piridine, in presence of piperidine.

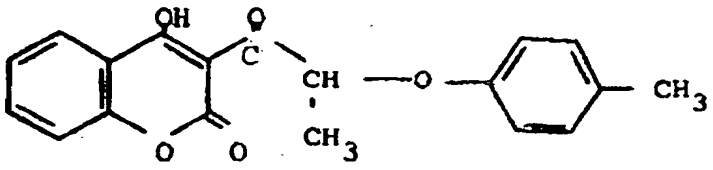
According to the invention, the products possess a potent anticoagulant and antitrombotic activity that has been evidenced in both the rat and in the rabbit.

These products can be used as antitrombotic agents for the prevention and treatment of trombolitical and coronary diseases.

The following examples illustrate the invention without limiting its extent.

## Example 1

3-(4-methyl fenoxide isopropioline)-4-hidroxy coumarin



## Preparation

In 110 ml of anhydric piridine, introduce 12 drops of piperidine, 13.5gr. of 4-hidroxy coumarin and 23.3gr. of 2-(4-methyl fenoxide) - propioline. Heat same during 3 hours at 95° ± 5°C. Once same returns to room temperature, slowly pour the reactional mixture into 700 ml of HCl 2N and 350gr. of ice. A brown precipitate becomes generated which isolates by filtration. The product is to be crystallized in absolute ethanol (330 ml) in presence of active coal. Accordingly, 10.6gr. of a beige product is obtained.

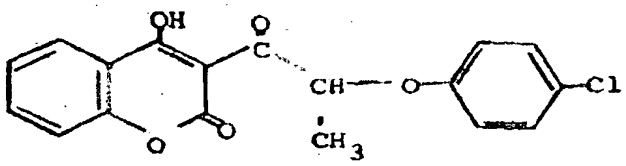
## Analysis

Point of fusion: 155-156°C

Analysis:

Spectrum of RMN at 200 MHz: see figure 1

## Example 2



## Preparation

The method of preparation is identical to that of example 1. By causing the 2-(4-chlorofenoxide)-propioline chloride to react in the hidroxy-4-coumarin, a beige product with a yield of 51% is obtained after the crystallization process in butanol.

## Analysis

| | |
|---|---|
| Point of Fusion: | 179-180°C |
| Valuation of the chloride: | 10.42% (theory: 10.3) |
| Spectrum of RMN at 200 MHz: | see the figure 2 |

## Anticoagulant Activity

The measurements taken in the rat and the rabbit were sampled amongst a homogeneous batch of 6 animals.

The product has been administrated by mixing same with corn starch, in suspension in an Arabic gum mucilage.

Blood from the anesthetized animal is taken and the Quick time is then determined in the plasma, according to the customary technique. A previous calibration, effected in a witness plasma, enables one to

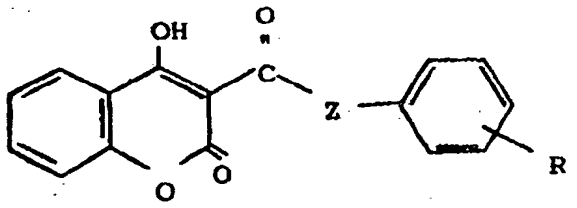
evaluate the degree of protrombine, and for a given dose, the curve indicating the decrease in the degree of protrombine can be plotted against a time interval.

This hypotrombinante action characterizes the antivitamin K activity of the products comprised in the invention.

The curves obtained show the great activity of these products characterized for an active dose of approximately 0.2 mg/kg in the rabbit and of 2 mg/kg in the rat (figures 3 and 4).

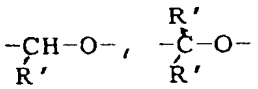
## Claims

1. New acylate derivatives of the hidroxy-4-coumarin of the general formula (I)



(I)

wherein
z can be - $(CH_2)_n$-, -$(CH_2)_n$-O-,

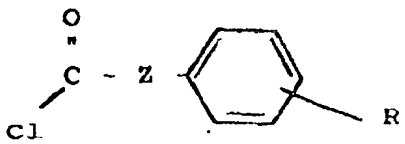


n mea 1 or 2
R' means $CH_3$ or $C_2H_5$
R can be H, $CH_3$, $C_2H_5$, Cl, Br, F, $NO_2$, $CH_3$ endowed with anticoagulant and antitrombotic properties.

2. 3-(4-methyl fenoxide isopropioline)-4-hidroxy coumarin

3. 3-(4-chloro fenoxide isopropioline)-4-hidroxy coumarin

4. Procedure for the preparation of the new acylated derivatives of hidroxy-4-coumarin of the general formula (I) indicated in the replevy 1, characterized because it involves acylatir.j hidroxy-4-coumarin with an acid formula chloride



wherein Z and R are defined as previously mentioned preferably in piridine and in the presence of piperidine.

5. Medicines based on the principle antivo of the general formula (I), useable as antitrombotic agents for the prevention and treatment of arterial and venous trombosis.

6. Medicines that contain as their main active 3-(4-methyl fenoxide isopropioline)-4-hidroxy coumarin.

7. Medicines that contain as their main active 3-(4-chloro fenoxide isopropioline)-4-hidroxy coumarin.

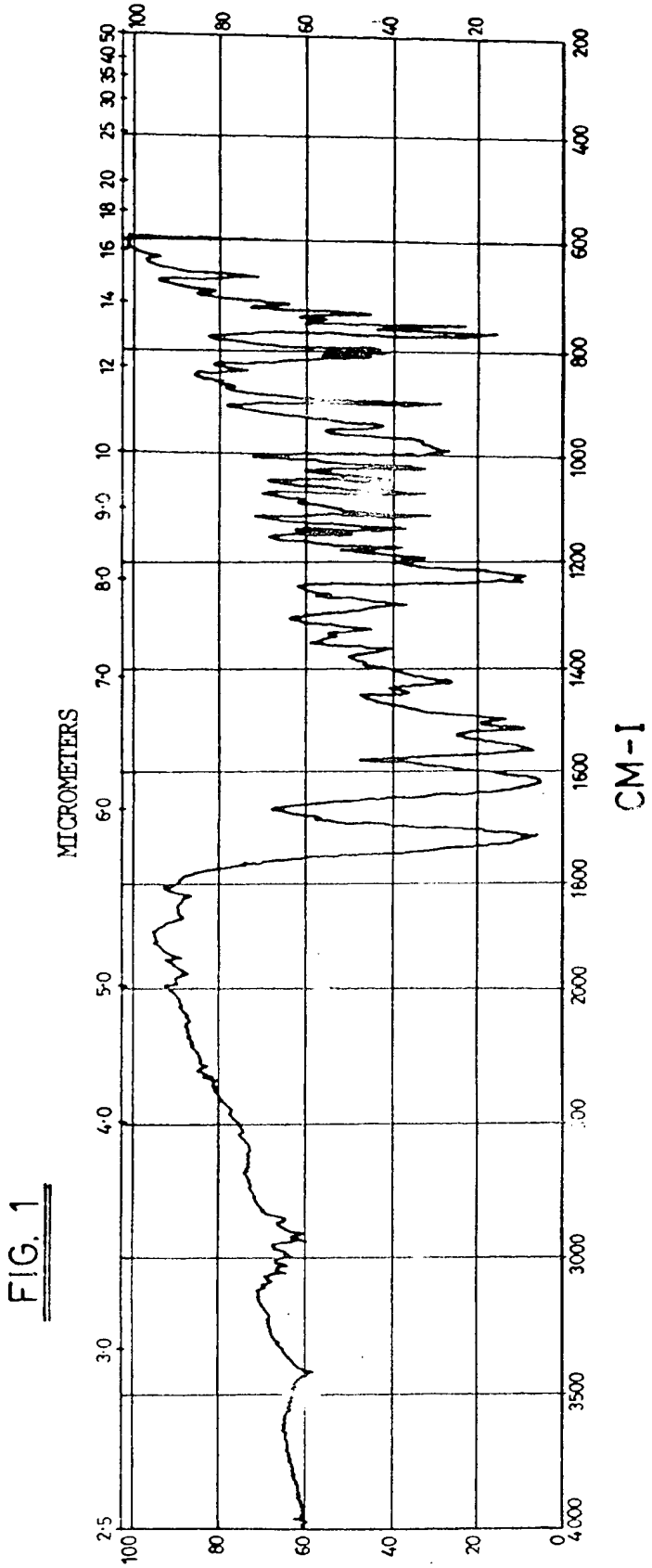



FIG. 1

FIG. 2

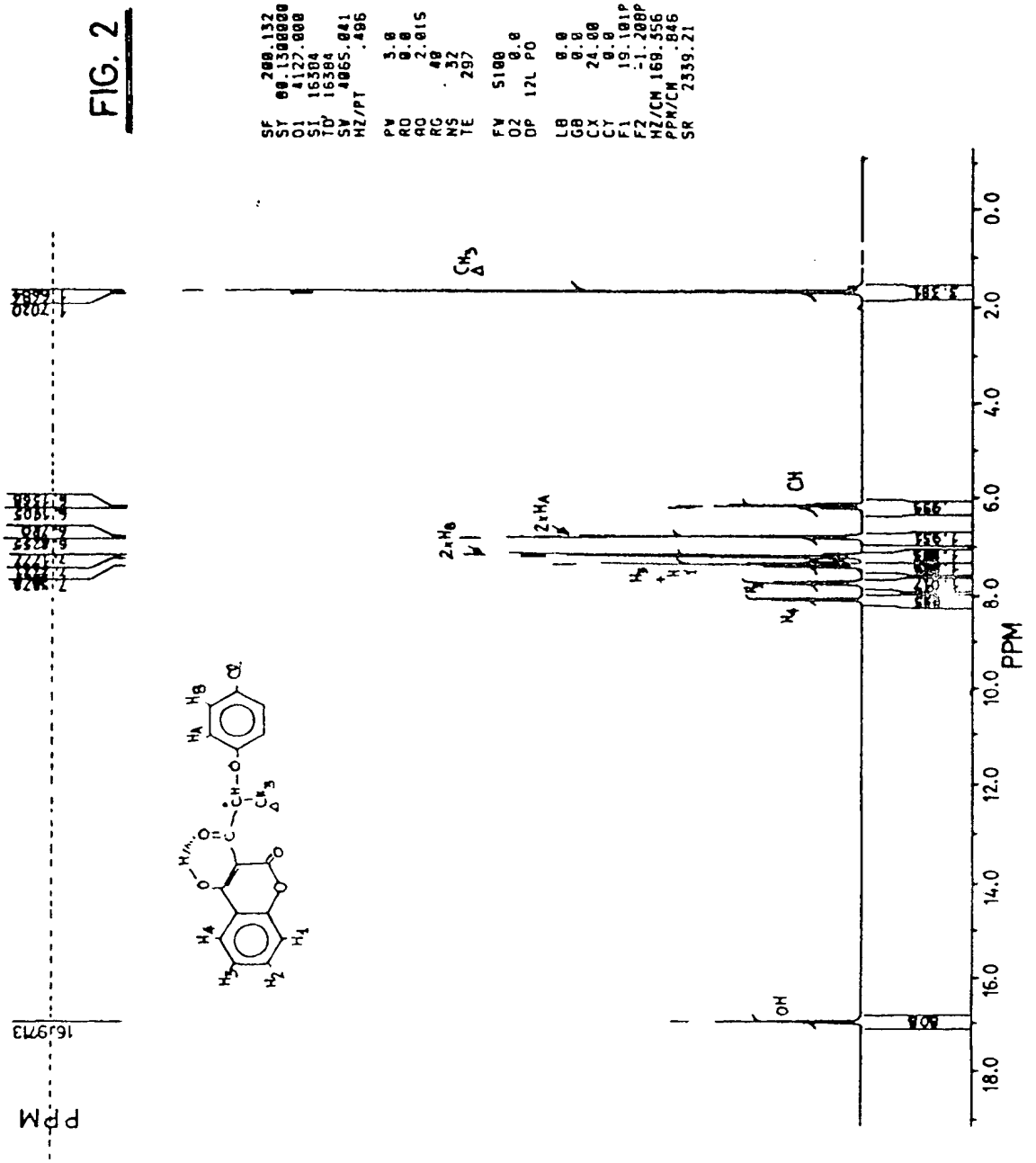

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FIG. 3

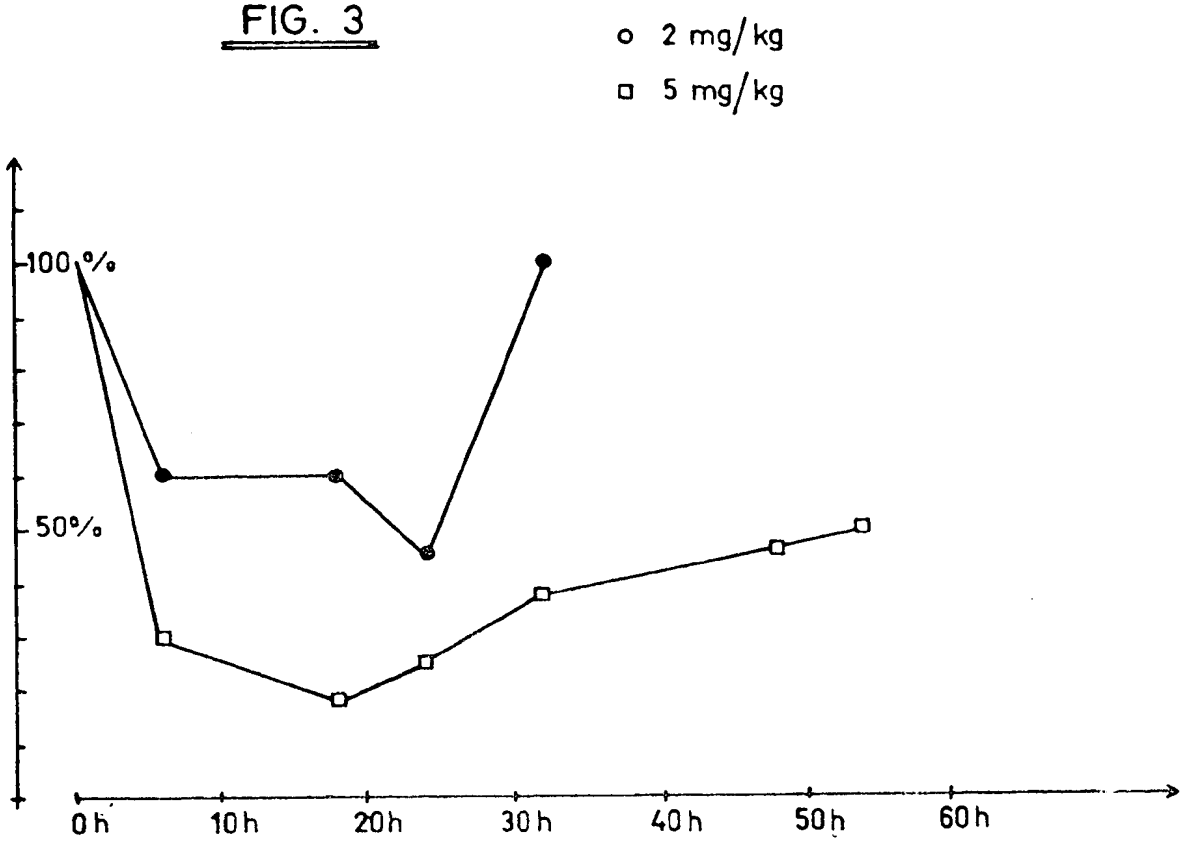
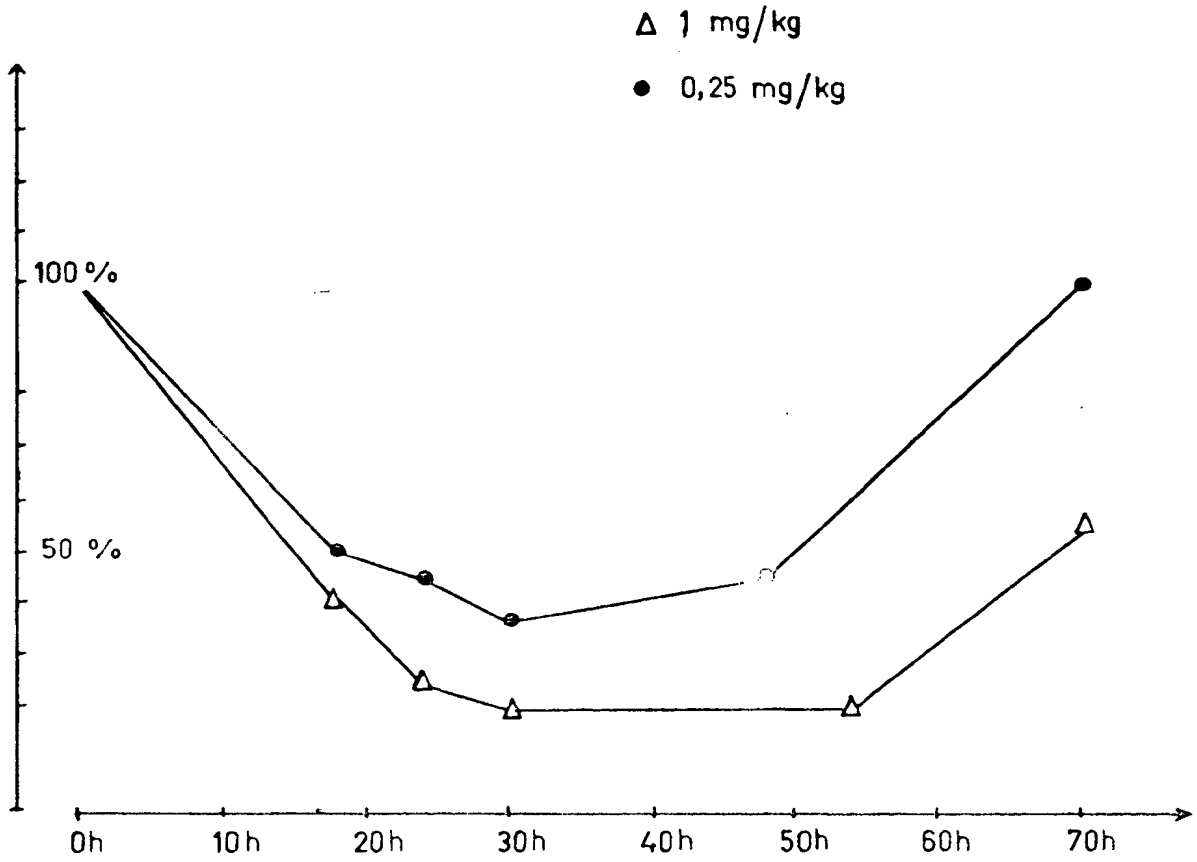


FIG. 4



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# EUROPEAN SEARCH REPORT

Application Number

EP 92 50 0036

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
|---|---|---|---|
| X | CHEMICAL ABSTRACTS, vol. 83, no. 25, 22 December 1975, Columbus, Ohio, US; abstract no. 206102g, page 378 ; & JP-A-50 046 666 (TORAY INDUSTRIES) 25 April 1975 * abstract; and Chemical Substances Index, page 6869CS, compounds with CAS Registry Nos. 57339-71-6, 57339-69-2, 57339-67-0; page 6887CS, Registry No. 57339-61-4 * | 1,5 | C07D311/46 A61K31/35 |
| X | CHEMICAL ABSTRACTS, vol. 98, no. 13, 28 March 1983, Columbus, Ohio, US; abstract no. 102730d, page 222 ; & CS-B-200 796 (J. HUBINEK) 15 June 1976 * abstract * | 1 | |
| A | US-A-2 427 578 (M.A. STAHMANN et al.) * the whole document * | 1,5 | TECHNICAL FIELDS SEARCHED (Int. Cl.5) |
| A | GB-A-1 175 808 (LABORATIORES LAROCHE NAVARRON) * page 1 * | 1,5 | C07D |
| A | GB-A-2 055 831 (REANAL FINOMVEGYSZERGYAR) * page 2 * | 1 | |

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 03 MARCH 1993 | RUSSELL F. ENGLISH |

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